REMARKS

Applicant respectfully requests reconsideration of the present application in view of the reasons which follow.

Claims 3-5 are cancelled. Claim 14 is amended. New claims 15-21 are added. Claims 14-21 are pending in this application.

Applicant requests that the examiner enter these amendments and new claims because no new matter has been added. Support for the amendments to claim 14 can be found in the specification at page 13, lines 10-19; page 3, lines 6-7 and lines 15-18; page 71, lines 10-15; page 12, lines 9-12; and finally, in the Table on pages 72 and 73. Additionally, support for new claims 15 and 18 can be found in the specification on page 4, lines 33-37. Support for new claims 16 and 17 can be found in the specification at page 13, line 35 through page 14, line 11 and page 13, lines 20-23, respectively. Support for new claims 19, 22, and 23 can be found in the specification on page 14, lines 15-34 and support for new claims 20 and 21 can be found in the specification on page 15, lines 1-4.

Rejection under 35 USC § 112, second paragraph

The examiner has rejected claims 3-5 and 14 for failing to point out and distinctly claim the subject matter of the invention.

As stated above, applicant has cancelled claims 3-5 and amended claim 14 to clarify the subject matter which the applicant regards as the invention.

Applicant first addresses the examiner's concern regarding the phrase "primary design antibody" and the specification's definition for this phrase. Claim 14, step (1) is a step for preparing a "primary design antibody". The primary design antibody is a conventional humanized antibody. To clarify the subject matter of claim 14 the phrase "primary design antibody" has been replaced with "humanized antibody" (Specification page 13, lines 10-19; page 3, lines 5-7 and 15-18; page 71, lines 10-15, and lines 72-73). In step (1), CDRs of humanized antibody (conventional humanized antibody) are CDRs from a first animal, and FRs are FRs from a second animal (human), but one or more amino acids in at least one of the FRs are substituted with amino acid residues present at the corresponding positions of the first animal

so as to maintain the antigen binding activity (specification page 3, lines 3-14). Applicant finds support for these amendments to claim 14 not only on page 13, lines 10-19 as the examiner pointed out in the outstanding office action, but also on page 3, lines 6-7 and 15-18, page 71, lines 10-15 (the step for preparation of the primary antibody in Example 1), the Table on pages 72 and 73, and on page 12, lines 9-12.

In response to the examiner's confusion concerning whether the humanized 'primary design antibody' of claim 14 is further humanized, Applicant affirms that the humanized antibody of claim 14 is further humanized by the method taught by claim 14. More specifically, a humanized antibody obtained in the step (1) is a conventional humanized antibody, i.e., a primary design antibody. The FR of this antibody is derived from a second animal, i.e., human, one or more amino acid residues of which have been substituted. Hence, the FR in the humanized antibody obtained in the step (1) is not a naturally occurring human FR. Therefore, according to the present invention, the FR in the humanized antibody obtained in step (1) is further humanized.

The amendments in step (2) and step (3) clarify that the FR subjected to the homology search is the FR in which one or more amino acid residues have been substituted in the humanized antibody of step (1). In fact, the homology search is carried out on all 8 FRs (including FRs in which amino acid has not been substituted) in the H chain and L chain. However, the FR subjected to the treatment in step (4) and step (5) is the FR in which one or more amino acids have been substituted. Claim 14 has been amended to clarify this process.

The amendment to step (4) further clarifies the characteristics possessed by a naturally occurring human FR ("natural FR") selected as a result of the homology search. Specifically, the FR selected for design of humanized antibody to be produced by the present invention has an amino acid residue substituted in the FR of the humanized antibody obtained in step (1) at the corresponding position(s), and has the same amino acid sequence as the FR of the humanized antibody obtained in step (1) or has a sequence with high homology with the FR of step (1) (Specification page 74, lines 2-30 and page 11, lines 8-28). Newly amended claim 14 clarifies this process.

In step (5), the amino acid sequence of the natural FR selected in the step (4) is compared with the amino acid sequence of the humanized antibody FR obtained in step (1). In the case where amino acid residues at corresponding positions are different, the different amino acid(s) in the amino acid sequence of the FR of the humanized antibody obtained in step (1) are substituted with a corresponding amino acid(s) in the selected natural FR in step (5). This second substitution produces a copy of a naturally occurring human FR (Specification page 74, line 31 - page 75, line 4, and page 11, lines 8-28). Claim 14 as presently amended clarifies this method step.

Additionally, the examiner objects to the expression "artificial amino acid residues." This phrase is replaced in step (1) ii) of the proposed claim 14 with a detailed description explaining the presence of the substituted amino acids. The term "artificial amino acid residues" does not mean "unnatural amino acids" or "mimetics" as suggested by the examiner. Rather, as explained above, the humanized antibody obtained in step (1) is a conventional humanized antibody. A conventional humanized antibody comprises CDRs of a first animal and FRs of a second animal (human). Usually, one or more amino acid residues in the human FRs in a conventional humanized antibody have been substituted with amino acids in FRs of the first animal so as to maintain the antigen binding activity (Specification page 3, lines 3 to 14). The amino acid residues introduced by the substitution were referred to as "artificial amino acid residues". For clarity, the designation "artificial amino acid residues" was replaced by a more detailed description of the method step.

The examiner also objected to the use of the phrase "homology search for the FR of a primary design antibody" because "it is unclear if the FR chosen is chosen to contain the residues that were originally in the human FR in part (1) or contains the residues that were substituted and as 'artificial amino acids.'" Applicant amended step (4) to clarify that the "homology search" identifies the FR containing the substituted amino acids. Specifically, step 4 is amended to state that the FR selected in the step (4) is (a) a naturally occurring human FR (natural FR), (b) has an amino acid introduced by substitution in the step (1) at the corresponding position as described in step (4) i), and (c) has an amino acid sequence the same as that of the FR obtained on the step (1) or has an amino acid sequence having high homology with the FR sequence of the humanized antibody obtained in the step (1) as described in the step (4) ii).

The examiner further found that "it is still unclear what the homology search obtains." Applicant amended steps (2) through (4) to clarify what the homology search identifies in steps (2) through (4). Specifically, the homology search in step (2) provides candidate natural human FRs which have high homology with the FR in the humanized antibody obtained in step (1). The homology search in step (4) identifies an FR having an amino acid sequence the same as that of the FR obtained in the step (1) or having an amino acid sequence having high homology with the FR sequence of the humanized antibody obtained in step (1) as selected from the candidate FRs obtained in the step (2).

Lastly, in response to 35 USC § 112, second paragraph, Parts a –c rejections in the Office Action dated January 15, 2003, applicant points out the claim amendments should overcome these parts of the rejection. Specifically, with respect to Part a, the expression "natural humanized antibody" is not used in the proposed amended claim 14, but corresponds to the "humanized antibody" in the first line of the proposed amended claim 14. Please note that one natural humanized antibody contains a total of 8 FRs (4 FRs in the H chain and 4 FRs in the L chain). Applicant has also addressed Part b, specifically the examiner's concerns regarding the phrase "artificial amino acid residues," in the proceeding arguments. Finally, in response the examiner's concerns in Part c regarding claim 14 presenting incomplete method claims, applicant has amended claim 14 to include steps (6) to (8).

Applicant believes that amended claim 14 satisfies the 35 USC § 112, second paragraph requirements.

Rejection under 35 USC § 103 (a)

Sato and Queen

The Sato reference, with or without Queen, fails to teach the invention of claim 14.

The Sato reference does not teach all of the steps provided by the method disclosed in claim 14. Specifically, the Sato reference does not extend beyond step (1) as taught by pending claim 14. According to Sato, CDR is grafted to a mouse monoclonal antibody, and one or more amino acid resides are substituted resulting in a humanized antibody. This product

corresponds to the humanized antibody of step (1) of the present invention. However, Applicant's invention teaches four additional modifications, steps (2) through (5), that Sato does not disclose or suggest.

Specifically, regarding V_L in human FR (REI), amino acids at the positions 39 and 71 are substituted with amino acids at the corresponding positions (positions 39 and 71) of mouse monoclonal antibody (Sato, page 377, Fig, 4 (A), and page 378, the left column, lines 2 to 4). Regarding VHF in human FR (HSG-I), amino acid residues at the positions 28, 30 and 71 are substituted with amino acid residues at the corresponding positions (positions 28, 30 and 71) of mouse monoclonal antibody (Sato, page 377, Fig. 4 (B)(1), and page 379, the left column, lines 10 to 13); and in human FR (HAX), an amino acid residue at the position 71. is substituted with an amino acid residue at the corresponding position (position 71) of mouse monoclonal antibody (Sato, page 377, rig. 4 (B)(2), and page 379, the left column, second paragraph, lines 10 to 11). Therefore, human FR of a humanized antibody of the Sato reference contains amino acid residue(s) derived from a mouse FR sequence. Therefore, resulting FR sequences (Sato page 377, Fig 4 (A), RV1; Fig 4 (B)(1), RVh1220 a to d and Fig. 4 (B)(2), sle122OH a to d) are artificially prepared FRs, and are different from the natural human sequences on page 377, Fig. 4 (REI, HSGI and HAX, respectively). In addition, it is not clear in the Sato reference whether or not the resulting artificial FRs are the same as the FRs of other human antibodies.

If the present invention is explained according to the Sato process, the present invention starts from the final product of the Sato reference, which is a reshaped human antibody (Sato, page 371, Abstract, lines 2 to 3, etc). The final product, the reshaped human antibody of the Sato reference, is an antibody formed by RV1 and one of RVh122 a to d or sell22OH a to d. These FRs include amino acid residues derived from mouse antibody as explained above so as to maintain the antigen binding activity. The above-mentioned FRs are called "artificial FRs for convenience of explanation.

Unlike Sato, the method of the present invention does not end its modification with the reshaped human antibodies taught in step (1). Rather, the method of claim 14 conducts the homology search taught in steps (2) through (4). Specifically, in steps (2) through (4) natural human FRs are identified which have the same amino acid residues as those substituted

in step (1) and which have high homology to the substituted FR of step (1). For example, in the case of RV1, a natural human FR would be identified that had the same amino acid residues as positions 39 and 71 on RV1 and that had high homology to RV1. Further, the method of the present application includes a possible second substitution on the FR of step (1) to replace the amino acid residues that differ between it and the natural human FR with the amino acid residues present in the natural human FR. Therefore, the final product is a "fully humanized" antibody with absolutely no mouse amino acid residues.

Similarly, the Queen reference does not teach the homology searches nor the possible second substitution taught in steps (2) through (5) of the present application. The Queen reference, like the Sato reference, describes how to determine which amino acid positions should be modified in step (1), but does not teach any method steps extending beyond this initial modification. Because neither the Queen reference nor the Sato reference teach the four additional method steps disclosed in claim 14, they cannot anticipate the present invention.

Additionally, in response to the applicant's statement that "the prior art does not result in a fully humanized antibody", the examiner stated that "the prior art does result in a fully humanized antibody as defined in the prior art." We believe that the meaning of "fully humanized" is clear from the above-mentioned explanation. However, regardless of semantics, it is clear that the method steps taught by claim 14 provide an antibody that is more humanized that the antibodies of the prior art. The homology search for the natural human FR region followed by the second substitution provides an antibody that not only has improved binding, resulting from the first substitution in step (1), but also has decreased patient rejection because of its fully humanized construction.

Finally, the examiner stated that "the claims do not recite maintaining the binding ability". In response, claim 14, step (1) ii), was amended to add the phrase "to maintain antigen binding ability."

Co and Queen

The combination of the Co reference and the Queen reference does not teach the invention of claim 14.

Similar to the Sato reference discussed above, the Co reference does not teach the additional method steps, steps (2) through (5), taught by the present invention. Specifically, the final product, humanized antibody, of the Co reference corresponds to the humanized antibody obtained in the step (1) of the proposed claim 14. According to Co, CDR is grafted to a mouse monoclonal antibody, and one or more amino acid residues are substituted resulting in a humanized antibody, which corresponds to the humanized antibody of the step (1) of the present invention (see, page 2871, the paragraph 1, lines 12 to 15, the same page, the paragraph 2, lines 8 to 13, and page 2S70, Fig. 1, and its explanation, lines 5 to 6). As stated above, the additional modifications corresponding to claim 14 steps (2) through (5) of the present invention are not performed by the method disclosed in the Co reference. Because neither Co nor Queen teach the four additional steps disclosed in claim 14, they cannot anticipate the present invention.

Roguska and Queen

The combination of the Roguska reference and the Queen reference does not teach the invention of claim 14.

The Roguska reference describes two humanized antibodies, GN9Olv.l.1 and GN9Olvl.O. In the humanized antibody GN901v,1.1, all FRs are natural human FRs (see, page 898, the left column, GN9O1.1.1). These FRs are "fully humanized FRs". However, for example, for the L chain, V region, FR does not contain, at the positions 3, 53 and 100, which are considered to be substituted with corresponding mouse amino acids, amino acid residues derived from mouse monoclonal antibody. Therefore, the GN9O1v.l.1 is different from humanized antibodies obtained by the present invention, at the positions 3, 53 and 108. F in the humanized antibody GN9O1V.1.1 "by chance" corresponds to naturally occurring human FR, i.e., KV2F. In this connection, please note that the Roguska reference states that it is very rare that humanized antibody is prepared by merely grafting mouse CDR onto a human monoclonal antibody (see, page 898, the left column, lines 12 to 8 from the bottom).

In the humanized antibody GN9O1V.1.O, for example regarding the L chain, V region, its FR contains at the positions 3, 2 and 108, Val, Arg and Gln, respectively. For the positions 3, 52 and 108, it is considered that substitution is necessary to maintain the antigen binding activity. Therefore, the humanized antibody GN9O1v.1.0 corresponds to the humanized

antibody obtained by the step (1). The Roguska reference does not describe nor suggest the additional method steps (2) through (5) disclosed in amended claim 14.

Therefore, the combination of the Roguska reference and the Queen reference does not anticipate the method disclosed by the present invention.

In light of the foregoing arguments, applicant argues that the present invention is not obvious from the teachings of the cited reference.

Applicant believes that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

The examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

If any fees are due in connection with the filing of this Amendment, please charge the fees to our Deposit account No 19-0741. If a fee is required for an extension of time under CFR § 1.136 that is not accounted for above, such an extension is requested and the fee should also be charged to our Deposit Account.

Respectfully submitted,

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